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Cu(I)/TEMPO-catalyzed aerobic oxidative synthesis of imines directly from primary and secondary amines under ambient and neat conditions

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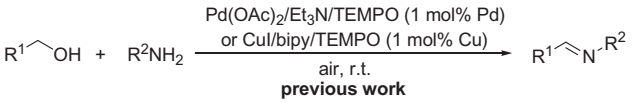
ABSTRACT

By catalyst and condition screening, a simple Cu(I)/TEMPO-catalyst system was found to be an active and highly effective catalyst for the aerobic oxidation of amines to imines in open air at room temperature under neat conditions. This new method provided a mild, efficient, and practical alternative for the synthesis of the useful imines directly from primary and secondary amines.

Because imines contain a reactive C=N double bond and can readily undergo various types of transformations such as reduction, addition, cycloaddition, and multi-component reactions, they are useful nitrogen sources and versatile intermediates in the synthesis of biochemically and pharmaceutically active compounds and natural products.[1] Traditionally, imines were prepared by dehydrative condensation of amines with carbonyl compounds, especially the aldehydes.[2] However, since aldehydes are reactive, odorous, toxic, readily oxidized to carboxylic acids, and not easy to handle and store, they usually require purification before use and inert and harsh reaction conditions. Since aldehydes and ketones are mostly obtained from corresponding alcohols via oxidation reactions, several tandem processes have recently been developed for preparation of imines from alcohols and amines.[3–6] For example, the early methods used excess amounts of oxidants such as MnO_2.[3] The dehydrogenative methods were conducted under inert conditions at high temperatures, generating gas hydrogen as the byproduct.[4] The presently available aerobic methods generally require the use of pure oxygen at elevated temperatures.[5] Worth noting is that, we recently developed two especially active Pd and Cu catalysts, which can efficiently catalyze the aerobic reactions of alcohols and amines in open air at room temperature to afford the useful imines Eq. 1.[6] To our knowledge, these may be the mildest methods ever known for imine synthesis from alcohols and amines.[3–6]



(1)

During studies, we found that both Pd and Cu catalysts can selectively oxidize the alcohols to aldehydes and generate the cross imines as the sole product Eq. 1,[6] without detecting any other potential byproducts derived from the oxidation reactions of amines.[7–9] On the contrary, when the Cu-catalyzed reaction was accidentally conducted under similar conditions without adding alcohol, it readily afforded 75% yield of the amine-derived imine **2a** with 12% yield of benzonitrile **3a** Eq. 2. In fact, various metal catalysts have been used to catalyze the aerobic oxidation of amines for the synthesis of nitriles,[7] amides,[8] and imines.[9] Among imine formation methods, most reactions still require the use of noble metal catalysts under oxidant-free conditions at high temperatures,[10] or large excess amounts of oxidants that will also generate large amounts of wastes,[11] or using pure oxygen as the oxidant at high temperatures.[9a–h] In contrast, practical methods that can use air as the more economic and safer oxidant and those which can be carried out under milder conditions are still rare up to date,[9i–m] and are thus still highly desirable in the field.[9n]

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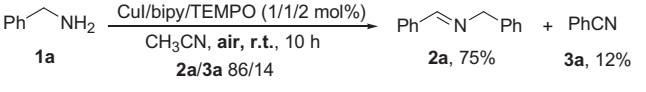
Therefore, the above interesting results Eq. 2 intrigued us to further investigate the Cu-catalyzed aerobic amine oxidation reaction to develop a mild and practical method for the synthesis of the useful imines directly from amines. Besides, although several Cu-catalyzed reactions have been reported,[9b,k–m] a mild and efficient Cu(I)/TEMPO-catalyzed method was not known yet.[12] Herein we report a new method for imine synthesis by describing a mild and efficient Cu(I)/TEMPO-catalyzed aerobic amine oxidation reaction in open air at room temperature under ligand- and solvent-free conditions.



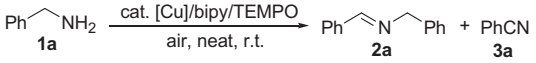
(2)

Since considerable amounts of benzonitrile **3a** was also generated as the byproduct Eq. 2, the conditions of the above reaction were further optimized to enhance the yield and selectivity of the target imine **2a** (Table 1). We found the reaction was better to be carried out under solvent-free conditions, for higher yield and higher selectivity of **2a** could be achieved without using the solvent (run 1). Preliminary screening on the loadings of CuI and bipy (2,2′-bipyridine) revealed that more loading of the ligand was ineffective to promote the reaction (run 2), but more loading of CuI could slightly enhance the product yield (run 3). A detailed screening on the loadings of CuI, bipy, and TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxyl) was then carried out to investigate their effects on the reaction. Thus, CuI alone, CuI/bipy, TEMPO alone, or bipy/TEMPO were all found to be inefficient to catalyze the reaction under similar conditions (runs 4–7). In contrast, CuI/TEMPO was found to be most effective so that 2 mol % only could ensure a high conversion of **1a** (97%) and high yield and high selectivity of **2a** under the same condition (run 8), which is even better than the reaction using bipy as the ligand (run 3). All the above contrastive results clearly showed that ligand bipy is unnecessary for the reaction, as well as the high catalytic activity of CuI/TEMPO in the reaction. Further condition screening showed that less loadings of CuI and/or TEMPO were less effective and more loadings of them were also unnecessary. During condition screening, we also investigated other Cu catalysts under the same condition. Thus, other Cu(I) catalysts such as CuBr (run 9) and CuCl (run 10), Cu(II) catalysts such as $CuBr_2$ (run 11),[12] $CuCl_2{\cdot}2H_2O$ (run 12), $Cu(OAc)_2{\cdot}H_2O$, $CuSO_4$, $Cu(NO_3)_2$, etc., were all found to be less effective catalysts than CuI for giving lower yields and/or lower selectivities of **2a**. In comparison with other Cu-catalyzed methods that require either a high temperature,[9k] or using dioxygen as the oxidant,[9b] or using higher loadings of catalysts, or large amount of solvents,[9b,l,m] or using complex catalyst systems,[9b,m] the present method may be a much simpler and more practical alternative since the reaction can be readily conducted under ambient and neat conditions by using lower loadings of the catalysts and air as the oxidant.

The optimized condition (Table 1, run 8) was then applied to various primary amines to extend the scope of the method.[13] As shown in Table 2, the results revealed that the method is highly tolerant of various functional groups. Thus, both electron-rich and -deficient benzylamines (runs 1–14), even the sterically more hindered *ortho*-substituted ones (runs 4, 7, 10, 13, 14), usually reacted efficiently at room temperature to give the target imines in good to high isolated yields and high selectivities (up to 98:2). Possibly due to the presence of two chloro groups, 2,4-dichlorobenzylamine (**1n**) gave a lower yield and lower selectivity of the product imine **2n** (run 14). However, the fluoro- and chloro-substituted imines obtained from the corresponding halo-benzylamines should be of potentially wide utility in synthesis due to the presence of the useful fluoro or chloro groups along with the reactive C=N moiety in the molecule. Besides, according to GC analysis of the reaction mixtures, no other byproducts (such as another potential byproduct, the corresponding aldehydes) were observed in the reactions, which may be attributed to the mild and neat conditions employed in the present method.

Similar to benzylamines, the reactions of heterobenzylamines **1o** and **1p** were also efficient under the same condition, but the target imines **2o** and **2p** could not be isolated pure at present (runs 15, 16), because they easily hydrolyzed to give the corresponding

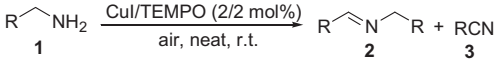
Table 1
Optimization of the reaction conditions[a]



Run	[Cu], [Cu]/bipy/TEMPO (mol %)	*t* (h)	**2a**[b] (%)	**3a**[b] (%)	**2a**/**3a**[c]
1	CuI, 1/1/2	10	80	6	93/7
2	CuI, 1/2/2	10	79	6	93/7
3	CuI, 2/2/2	10	82	8	91/9
4	CuI, 2/0/0	31	9	—	—
5	CuI, 2/2/0	12	20	—	—
6	CuI, 0/0/2	10	NR[d]	—	—
7	CuI, 0/2/2	10	NR	—	—
8	***CuI, 2/0/2***	***10***	***91 (85)***	***6***	***94/6***
9	CuBr, 2/0/2	12	81	12	87/13
10	CuCl, 2/0/2	12	68	25	73/27
11	$CuBr_2$, 2/0/2	12	15	—	—
12	$CuCl_2$,[e] 2/0/2	12	2	—	—

[a] The mixture of benzylamine **1a** (5.0 mmol), Cu catalyst, bipy, and TEMPO was directly stirred in open air at room temperature (ca. 30 °C), and was then monitored by GC–MS and/or TLC.
[b] GC yields (isolated yields in parenthesis) were based on **1a**.
[c] Compound **2a**/**3a** ratios were obtained by GC analysis.
[d] NR: no reaction.
[e] $CuCl_2{\cdot}2H_2O$ was used.

Table 2
Extension of the substrate scope[a]



Run	RCH_2NH_2 (**1**)	*t* (h)	**2**%, **2**/**3**[b]
1	$PhCH_2NH_2$ (**1a**)	10	**2a**: 91 (85), 94/6
2	4-$FC_6H_4CH_2NH_2$ (**1b**)	20	**2b**: 92 (82), 96/4
3	3-$FC_6H_4CH_2NH_2$ (**1c**)	16	**2c**: 95 (89), 96/4
4	2-$FC_6H_4CH_2NH_2$ (**1d**)	16	**2d**: 96 (87), 97/3
5	4-$MeOC_6H_4CH_2NH_2$ (**1e**)	20	**2e**: 94 (86), 96/4
6	3-$MeOC_6H_4CH_2NH_2$ (**1f**)	16	**2f**: 97 (88), 97/3
7	2-$MeOC_6H_4CH_2NH_2$ (**1g**)	16	**2g**: 92 (84), 96/4
8	4-$MeC_6H_4CH_2NH_2$ (**1h**)	16	**2h**: 85 (75), 97/3
9	3-$MeC_6H_4CH_2NH_2$ (**1i**)	17	**2i**: 96 (88), 97/3
10	2-$MeC_6H_4CH_2NH_2$ (**1j**)	17	**2j**: 94 (81), 96/4
11	4-$ClC_6H_4CH_2NH_2$ (**1k**)	16	**2k**: 88 (82), 98/2
12	3-$ClC_6H_4CH_2NH_2$ (**1l**)	17	**2l**: 85 (77), 98/2
13	2-$ClC_6H_4CH_2NH_2$ (**1m**)	24	**2m**: 95 (86), 98/2
14	2,4-$Cl_2C_6H_3CH_2NH_2$ (**1n**)	24	**2n**: 68 (51), 78/22
15[c]	(2-Furyl)methylamine (**1o**)	12	**2o**: 81, 81/19[d]
16[c]	3-Picolylamine (**1p**)	24	**2p**: 88, 95/5
17[c]	4-Picolylamine (**1q**)	24	**2q**: 37, 77/23
18[c,e]	*n*-$C_8H_{17}NH_2$ (**1r**)	48	**2r**: 73, 86/14
19[c,e]	$PhCH_2CH_2NH_2$ (**1s**)	48	**2s**: 49, 91/9[f]

[a] Unless otherwise noted, the mixture of **1** (5.0 mmol), CuI (2 mol%), and TEMPO (2 mol %) was directly stirred in open air at room temperature (ca. 30 °C), and was then monitored by GC–MS and/or TLC.
[b] GC yields (isolated yields in parenthesis) of **2** were based on **1**. **2**/**3** ratios were obtained by GC analysis.
[c] The target imines could not be isolated pure at present (see Ref. 14).
[d] The byproduct is the corresponding amide, 2-furancarboxamide.
[e] CuCl/TEMPO (2/2 mol %), air, neat, 60 °C.
[f] The byproduct is $PhCH{=}NCH_2CH_2Ph$ (see also Ref. 9j).